REMARKS

Claim Amendments

Claims 1-35 were previously withdrawn without prejudice as drawn to a non-elected invention. Applicant has amended claim 36 so that it is drawn to a method of cleaving RNA comprising SEQ ID NO:2460 using a chemically modified double stranded nucleic acid molecule having the following features: (1) it comprises a separate sense strand and antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; (2) each strand of the siRNA nucleic acid molecule is 18 to 27 nucleotides in length; (3) the antisense strand of the nucleic acid molecule comprises 18 to 27 nucleotides that are complementary to a target VEGFr1 RNA; (4) the sense strand of the nucleic acid molecule is complementary to the antisense strand, and comprises a portion of the target RNA sequence of about 18 to 27 nucleotides; (5) about 50 to 100 percent of the nucleotides in each of the sense and antisense strands of the nucleic acid molecule are chemically modified with modifications independently selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications; and (6) one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides.

Amended claim 36 is fully supported by the specification as filed, for example, inter alia, at pages 8-9, 10-13, 14-15, 16-17, 19, 20, 30-32, 33, 38-41, Figures 4 and 5, Tables I-IV.

In addition, claims 44, 45, 46, 49, 50, and 51 have been amended to clarify that 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of the specified purine or pyrimidine nucleotides has the specified modification. Support for the amendment is found in the specification at, for example, pages 30-32 and 38-41.

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Claim 44 has additionally been amended to recite that 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides in the sense strand are 2'-O-methyl pyrimidine nucleotides. Support for the amendment is found in the specification at, for example, 30-32 and 38-41.

In addition, the claims have been further amended merely to correct dependencies and other matters of form.

New claim 57 depends from claim 50 and recites a method using a double stranded nucleic acid molecule wherein additionally 1, 2, or 3 purine nucleotides in the sense strand are 2'-O-methyl nucleotides. Support for new claim 57 is found in the specification at, for example, 30-32 and 38-41.

New claim 58 depends from claim 36 and recites a method using a double stranded nucleic acid molecule wherein additionally the antisense strand includes a terminal phosphate group. Support for new claim 58 is found in the specification at, for example, pages 23 and 29.

New claim 59 depends from claim 36 and recites a method using a double stranded nucleic acid molecule wherein the nucleic acid molecule is in a pharmaceutically acceptable carrier or diluent. Support for new claim 59 is found in the specification at, for example, 21-22 and 66.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

A complete listing of all the claims, in compliance with the revised amendment format, is shown above.

Specification Objection

The specification has been objected to because the word "described" on page 12, line 12 of the specification has been misspelled. Applicant has amended the specification to correct the spelling of the word "described" and respectfully requests withdrawal of the objection to the specification.

Claim Objection

The Office has objected to claim 38 as being of improper dependent form because it allegedly fails to further limit the subject matter of claim 36. The Office argues that since the claim is drawn to an siRNA, the molecule by nature contains ribonucleotides. However, claim 36 has been amended to recite a chemically modified double stranded nucleic acid molecule, wherein, among other things, about 50 to 100 percent of the nucleotides in each of the sense and antisense strands of the nucleic acid molecule are chemically modified. Accordingly, the claim covers embodiments in which 100% of the nucleotides of the nucleic acid molecule are modified and may not be considered ribonucleotides. Applicant submits that claim 38 is of proper dependent form and respectfully requests withdrawal of the objection.

35 USC § 112, Second Paragraph Rejections

Claim 36 and dependent claims 37-56 have been rejected under 35 USC § 112, second paragraph, as being indefinite because claim 36 recites the phrase "doubled stranded ribonucleic acid (siRNA)" and the Office alleges that the term "siRNA" is not the proper abbreviation for "doubled stranded ribonucleic acid". Without acceding to the merits of the rejection, Applicant has amended claim 36 to substitute the word "nucleic" for "ribonucleic" and to delete the term "siRNA". Accordingly, the rejection is moot and Applicant respectfully requests withdrawal of the rejection.

Claim 37 has been rejected under 35 USC § 112, second paragraph, as being indefinite because claim 37 recites the phrase "the siRNA molecule comprises no ribonucleotides" and the Office alleges that an siRNA molecule by nature comprises ribonucleotides. Without acceding to the merits of the rejection, Applicant has cancelled

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claim 37, rendering the rejection moot. Applicant respectfully requests withdrawal of the rejection.

Claim 55 has been rejected under 35 USC § 112, second paragraph, as being indefinite because claim 55 recites the limitation "said 2'-deoxy-pyrimidine" in claim 54. Without acceding to the merits of the rejection, Applicant has cancelled claim 55, rendering the rejection moot. Applicant respectfully requests withdrawal of the rejection.

35 USC § 112, First Paragraph Rejection

The Office has rejected claims 36-56 under 35 USC § 112, first paragraph, for alleged lack of enablement. Claims 37, 39-43 and 53-55 have been cancelled. The Applicants respectfully traverse this rejection with respect to claims 36, 38, 44-52, 56-59.

The Office argues that the specification, while being enabling for a method of cleaving RNA comprising SEQ ID NO: 2460 encoded by a mammalian VEGFr1 gene *in vitro*, does not reasonably provide enablement for such a method *in vivo*. Specifically, the Office alleges that there is no guidance in the specification as filed that teaches how to cleave RNA comprising SEQ ID NO: 2460 encoded by mammalian VEGFr1 gene via contacting a siRNA with the RNA encoded by VEGFr1 gene by any other means except ocular injection *in vivo*. The Office further alleges that while the Applicant has demonstrated delivery via ocular injection in mice *in vivo*, the claims are not enabled for delivery of siRNA *in vivo* by the broadly recited methods, as delivery of siRNS duplexes is known in the art to be unpredictable. The Office cites Scherer et al, Mahato et al., and Zhang et al., for teaching the state of the art with respect to *in vivo* effectiveness of siRNA.

Under 35 U.S.C. §112, all that is required for satisfaction of the enablement requirement is that the specification describe the invention in such terms as to enable one skilled in the art to make and use the invention. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *US v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); M.P.E.P. §2164.01. The contours

of the "undue experimentation" standard have been outlined in several cases. The Federal Circuit has explained that "[t]he key word is 'undue' and not 'experimentation'. . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Moreover, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." MPEP 7th ed., rev. 2 § 2164.01 (citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983); see also *Massachusetts Institute of Technology vs. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985) and *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Thus, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue *In re Angstadt*, 537 F.2d 498 (CCPA 1976).

Contrary to the Office's allegation, the specification thoroughly teaches a method for cleaving RNA comprising SEQ ID NO: 2460 encoding by mammalian VEGFr1 gene using a chemically modified double stranded nucleic acid having the recited structural elements and chemical modifications. Specifically, the specification teaches one skilled in the art to make and use the claimed chemically modified double stranded nucleic acid molecules such that one could practice the inventive method.

The specification teaches the structural characteristics of the double stranded nucleic acid molecules recited in the claims used to cleave RNA encoded by VEGFr1. For example, the specification teaches the preferred size of the double stranded nucleic acid molecules throughout the specification and also teaches the recited chemical modifications at, for example, pages 8-9, 30-32, and 38-41, as well as Tables II-IV. The specification further teaches the sense and antisense structure of the double stranded nucleic acid at, for example, pages 8-9, 10-12, 12-13, 33, and 65.

In addition, the specification provides a detailed description of the methods used to make the double stranded nucleic acid molecules; that is, the design, synthesis and testing of the double stranded nucleic acid molecules used in the instantly claimed invention in appropriate biological systems. At pages 53-55, 57-63, 87-91, 116-117, Figures 7-10, and

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Table I the specification teaches one how to make (chemically synthesize) double stranded nucleic acid molecules, including molecules having the different chemical modification recited in the claims (pages 92-100, Figures 4 and 5, Tables II-IV). The specification further teaches that the nucleic acid molecules can be made using expression vectors at, for example, pages 111-113. The specification also teaches how to determine VEGFr1 target sites at, for example, pages 118-120 (Examples 2-4).

In addition, the specification teaches one how to use the claimed molecules and methods. First, the specification teaches various methods for modulating VEGFr1 gene expression, including down-regulating VEGFr1 gene expression, at pages 41-53 and 55-56 and teaches how to treat various diseases, such as tumor angiogenesis and cancers, using the double stranded nucleic acid molecules at pages 69-74 and 113-116. The specification further teaches one skilled in the art various methods for administering the double stranded nucleic acid molecules *in vitro* (pages 100-110, 125-126) and *in vivo* (pages 100-110, 126-131), provides dosages and formulations (pages 104-108), and teaches several methods for testing for RNAi activity (Examples 6 and 7, Figure 11).

Importantly, the specification teaches that VEGFr1 expression is associated with, inter alia, tumorigenicity and neovascularization and further teaches that tumorigenicity and neovascularization are involved in several disease states, including the maintenance and/or development of cancer and other proliferative diseases. The specification provides several examples of administration of double stranded nucleic acid molecules using appropriate *in vitro* and *in vivo* neovascularization and tumorigenicy models, and demonstrates RNAi activity in these models using the chemically modified nucleic acid molecules. Specifically, the specification teaches the use of the following *in vitro* and *in vivo* models:

(1) siRNA mediated inhibition of VEGF-induced angiogenesis in a rat corneal model of angiogenesis (Figure 12 and Example 10)

(2) reduction of VEGFr1 RNA in A375 cells by chemically modified siRNAs that target VEGFr1 (Figure 13 and Example 9)

(3) inhibition of VEGF induced neovascularizatiuon in a rat corneal model of VEGF induced angiogenesis using chemically modified siRNAs (Figure 16 and Example 10)

(4) inhibition of VEGF induced neovascularizatiuon in a mouse model of coroidal neovascularization via intraocular administration of chemically modified siRNA (Figure 17 and Example 10)

(5) inhibition of VEGF induced neovascularizatiuon in a mouse model of coroidal neovascularization via periocular administration of chemically modified siRNA (Figure 18 and Example 10)

(6) inhibition of VEGF induced neovascularizatiuon in a mouse model of coroidal neovascularization via periocular administration of chemically modified siRNA (Figure 19 and Example 10)

The specification also teaches several additional models at pages 126-131, including tumor angiogenicity, corneal models, hypoxia models, transgenic mice, glioblastoma models, Matrigel models, as well as several other models.

Despite the demonstration of efficacy of the claimed methods in several *in vitro* and *in vivo* models, the Office maintains that the specification is not enabling for the cleavage of VEGFr1 *in vivo* due to unpredictability in the art. However, Applicant has provided ample data and guidance in the specification to demonstrate the efficacy of the chemically modified double stranded nucleic acid molecules in appropriate *in vitro* and *in vivo* biological models.

One of ordinary skill in the art would have recognized that these cell and tissue models could be used as a predictive model for *in vivo* activity. As established by the Federal Circuit, "if the art is such that a particular model is recognized as correlating to a specific condition then it should be accepted as correlating *unless the Examiner has evidence that the model does not correlate.*" MPEP 2164.02 [emphasis added]; *In re*

Brana, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Thus, the described efficacy of double stranded nucleic acid molecules in an appropriate cell culture or animal model would have been readily accepted by a person skilled in the art to be reasonably predictive of the ability of these molecules to cleave target VEGFr1 sequences in cells and *in vivo*, and thereby be effective in an *in vivo* application. As further support for this position, the Federal Circuit has found that data showing the successful use of compounds as antitumor substances in tumor model systems were sufficient to enable the use of those compounds as anticancer drugs in animals. *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995).

The acceptance of the therapeutic use of double stranded nucleic acid molecules is further demonstrated by the FDA approval of several Investigational New Drug applications for inhibition of various targets, including VEGFr1. FDA approval provides further confirmation that treatment with double stranded nucleic acid is accepted by those skilled in the art as well as by the regulatory authority.

The Examiner alleges that trial and error experimentation would be necessary to practice the invention. However, Applicant points out that a considerable amount of experimentation is permissible, if it is merely routine. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Moreover, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed Cir. 1985); MPEP 7th ed., rev. 2 § 2164.01 (citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983). *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995).

Furthermore, the Federal Circuit has found that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). Using the methods known in the art and described in the instant application, a skilled artisan could easily formulate and test

double stranded nucleic acids *in vitro* and *in vivo* as a matter of routine experimentation. The fact that modified double stranded nucleic acids are being tested in clinical trials is further evidence that the amount of experimentation necessary to practice the invention is not undue.

Finally, Applicant points out that the Office fails to provide any evidence whatsoever that the instant invention would not work for its intended purpose, other than alleging that siRNA technology is an unpredictable art based on the Scherer et al, Mahato et al., and Zhang et al. articles. However, Applicant has provided ample data and guidance in the specification that demonstrate the efficacy of modified double stranded nucleic acid molecules both *in vitro* and *in vivo*. Accordingly, there is no reason to believe and the Office has not demonstrated that the claimed methods using a double stranded nucleic acid molecule to cleave VEGFr1 RNA would not have activity *in vivo*. In the absence of any technical reasons to support its reasoning, the Office has failed to establish a *prima facie* case of lack of enablement. M.P.E.P. § 2164.04.

For all of the reasons discussed above, the specification teaches one skilled in the art how to make and use the claimed invention. Accordingly, Applicant respectfully requests withdrawal of the enablement rejection under 35 U.S.C. § 112, first paragraph,

35 USC § 103 Rejections

Claims 36-40 and 44-55 stand rejected under 35 USC § 103 as allegedly obvious over Pavco et al. (US 6,346,398 B1), in view of Elbashir et al. (EMBO J., 20:6877-6888, 2001), Parrish et al. (Molecular Cell, Vol. 6, 1077-1087, 2000), Cook et al. (US 5,587,471), Hammond et al. (Nature, 2001, vol 2, pages 110-119) and Caplan (Expert Opin Biol Ther, 2003 Jul, 3(4), pp.575-86). Claims 37, 39-40 and 53-55 have been cancelled have been cancelled. The Applicants respectfully traverse with respect to claims 36, 38, 44-52 and 56-59.

The Office relies on Pavco et al. for its teaching of targeting flt-1, another name for VEGFr1, with ribozymes and antisense oligonucleotides. The Office also states that Pavco teaches chemical modifications, including 2'-O-methyl modifications,

phosphothioates and inverted abasic deoxyribose and further teaches that targeting flt-1 to decrease VEGF expression would be beneficial because VEGF is associated with tumor angiogeneisis and rheumatoid arthritis. The Office relies on Elbashir for its teaching of dsRNA duplexes 21-23 nucleotides in length and itsb teachings of 2'-deoxy and 2'-O-methyl modifications to one or both strands. (The Office states that Elbashir teaches complete substitution of one or both strands, but fails to note that Elbashir teaches AWAY from such molecule, as discussed below.) The Office relies on Parrish for teaching chemical modifications to long dsRNA, which is "necessarily cleaved into modified siRNA duplexes". Specifically, the Office alleges that Parrish teaches a dsRNA molecule of 18-27 nucleotides, particularly those over 26 bp. The Office relies on Cook for teaching various conjugates that can be incorporated into oligonucleotides, including glyceryl. The Office relies on Hammond for its general teachings regarding siRNA and RNAi.

The Office argues that it would have been obvious to substitute a siRNA duplex, as taught by Elbashir and Parrish, for the ribozyme or antisense oligonucleotide taught by Pavco et al. The Office further argues that it would have been obvious to incorporate 2'-O-methyl modifications, phosphorothioates, and inverted abasic deoxyribose as taught by Pavco, as well as 2'-deoxy, and 2'-O-methyl modifications to one or both strands as taught by Elbashir, and 2'-deoxy-2'-fluoro modifications as taught by Parrish into the siRNA molecule.

Under 35 U.S.C. § 103(a), to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143.

The cited references do not teach each and every element of the claims. None of the references teach or suggest a siRNA molecule that comprises 2'-O-methyl and 2'-deoxy-2'- fluoro modifications. Specifically, none of the cited references, alone or in

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combination, make obvious the chemically modified double stranded nucleic acid constructs recited in the claims, in which about 50 to 100 percent of the nucleotide positions in one or both strands of the nucleic acid molecule are chemically modified with 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and/or deoxyabasic modifications; AND one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides. Therefore, the references cannot render the instant claims obvious.

Contrary to the Office's allegation, none of the art, alone or in combination, provides any insight into whether highly modified double-stranded nucleic acid constructs, such as those recited in the claimed methods, would function. Indeed, Parrish and Elbashir expressly teach away from highly modified siRNA constructs. Parrish actually teaches away from siRNA having 2'-deoxy modifications and other chemical modifications of the antisense strand, both of which are shown to decrease RNAi activity in Parrish (see pages 1081 and 1082, Figures 5 and 6). Thus, Parrish teaches that modifications of the antisense strand decrease RNAi activity. Likewise, Elbashir teaches that extensive substitution with 2'-deoxy or 2'-*O*-methyl modifications abolishes RNAi. Therefore, neither Parrish nor Elbashir teach or suggest all of the elements of the claimed invention, that is, a double stranded nucleic acid molecule wherein about 50 to 100% of one or both strands are chemically modified and wherein the one or more of the purine nucleotides on either strand are 2'-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides on either strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides.

In addition, there is no suggestion or motivation to combine the cited references to arrive at the rejection of the claims. The Office alleges that one of ordinary skill in the art would be motivated to make a chemically modified siRNA targeted to flt-1 RNA since Pavco taught the use of antisense oligonucleotides and ribozymes to reduce the expression of flt-1. There is no motivation in Pavco to modify a single-stranded antisense molecule or a ribozyme molecule directed to flt-1 to a double-stranded, chemically modified siRNA molecule. In fact, the results of Pavco teach away from

modifying the antisense or ribozyme molecule to another structure, such as a chemically modified double stranded siRNA molecule, because Pavco reported the successful inhibition of flt-1 using a single-stranded antisense molecule and a ribozyme molecule.

None of the other references, including Elbashir and Parrish, even mention the VEGFr1 gene, much less teach a method of cleaving a VEGFr1 RNA using an extensively modified double stranded nucleic acid having the recited modifications. Thus, they provide no motivation to target the VEGFr1 gene using siRNA.

Furthermore, the cited references provide no motivation to use an extensively chemically modified siRNA molecule having 2'-O-methyl and 2'-fluoro modifications with a reasonable expectation of success. Parrish teaches that modifications of the antisense strand decrease RNAi activity. Likewise, Elbashir teaches that extensive substitution with 2'-deoxy or 2'-*O*-methyl modifications abolishes RNAi. None of the other references teach chemical modifications of siRNA molecules.

In the time period of about 2000-2001 the high potency of siRNAs (as compared to antisense and ribozymes) tended to suggest that no additional chemical modification of the molecules would be necessary. It was common knowledge to those skilled in the art at the time of the invention that single stranded RNA and DNA is much more susceptible to nuclease attack than double stranded nucleic acids. Thus, it was thought the relatively unstructured antisense and ribozyme nucleic acid molecules would be expected to require additional stabilization while the substantially double-stranded siRNA molecules would not. An example of this thinking is seen in the post filing art, as demonstrated by Elbashir I (EMBO Journal, 20:6877-6888 (2001); copy enclosed), where an emphasis was placed on modifying the 3' single stranded ends of the siRNA, with little effort made to modify the double stranded 5' ends. *See,* p. 6881, "*2'-deoxy- and 2'-O-methyl-modified siRNA duplexes*;" p. 6884, "*Sequence effects and 2'-deoxy substitutions in the 3' overhang.*"

The methods paper of Elbashir II (Methods 26:199-213 (2002)) best exemplifies the mindset of the day, that additional chemical modifications are unnecessary for effective RNAi activity. This paper gives specific instructions for designing and carrying out an RNAi experiment. On page 202, Protocol 1 (step 2) states that:

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> Independent of the selection procedure described in Fig. 2, synthesize the sense siRNA as 50-(N19)TT, and the sequence of the antisense siRNA as 50-(N'19)TT, where N'19 denotes the reverse complement sequence of N19. N19 and N'19 indicate ribonucleotides; T indicates 2'-deoxythymidine.

Thus, RNA duplexes with dTdT 3' ends were considered the correct substrate for carrying out RNAi experiments. The terminal TT was there primarily to make chemical synthesis easier and less expensive, although some minor protection from **single-stranded** ribonucleases was also considered a possibility (Elbashir I, Elbashir II). Finally, Elbashir II makes specific mention of four suppliers of siRNA duplexes for RNAi research; all four companies supply the reagents in the standard form described in Protocol 1 of Elbashir II.

As stated above, there was no motivation to seek chemically modified siRNAs during the period in question, so it comes as no surprise that only a few papers discuss the subject. Elbashir I is the only paper from the period that describes a significant attempt to modify siRNAs away from their own standard of RNA with TT overhanging ends. Their efforts are incomplete, but suggest that substantial modification will destroy RNAi activity. Under the heading "*The siRNA user guide*" (*see,* page 6885) Elbashir I provides guidance to those of ordinary skill in the art on the design of siRNA duplexes. This guide states:

> Efficiently silencing siRNA duplexes are composed of 21 nt sense and 21 nt antisense siRNAs and **must** be selected to form a 19 bp double helix with 2 nt 3'-overhanging ends. 2'-deoxy substitutions of the 2 nt 2'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNAse resistance of siRNA duplexes. **More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi**, probably by interfering with protein association for siRNAp assembly. (emphasis added).

This reference suggests that chemical modifications are generally not tolerated by siRNAs except for substitution of the 3'-terminal nucleotides of siRNA with deoxynucleotides. Further, modifications with 2'-O-methyl or other modifications were not tolerated. Additionally, Elbashir I showed that modifications beyond the 3'-terminal nucleotides of the siRNA were not tolerated.

Further, in the section entitled "*2'-deoxy- and 2'-O-methyl-modified siRNA duplexes*" (see pages 6881-6882), Elbashir I describes the effect of chemical modification on the activity of the siRNA duplex to mediate RNAi. The authors state:

> To assess the importance of the siRNA ribose residues for RNAi, duplexes with 21 nt siRNAs and 2 nt 3'-overhangs with 2'-deoxy- or 2'-O-methyl-modified strands were examined (Figure 4). Substitution of the 2 nt 3'-overhangs by 2'-deoxynucleotides had no effect and even the replacement of two additional ribonucleotides by 2'-deoxynucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Thus, 8 out of 42 nt of a siRNA duplex were replaced by DNA residues without loss of activity.

This suggests that the use of 2'-O-methyl substitutions in siRNAs was not tolerated. While 2'-deoxy substitutions at the 3'-terminal positions were permitted, there was no mention of any active siRNAs using 2'-O-methyl modifications, even at the terminal positions. Furthermore, because complete substitution of one or both siRNA strands with either 2'-deoxy or 2'-O-methyl residues resulted in a complete loss of RNAi activity, the results of Elbashir I suggests that modification of internal nucleotides positions reduced the ability of siRNAs to mediate RNAi, probably by interfering with protein interactions or siRNP assembly.

It was not until 2003 that reports began appearing in the scientific literature regarding the use of chemical modifications other than 3'-terminal 2'-deoxy substitutions in siRNAs. *See, e.g.,* Chiu and Rana, 2003, RNA, 9:1034-1048; Allerson *et al.,* 2005, *J. Med. Chem.* 48, 901. It is readily apparent from the publication record that those working in the RNAi field initially followed the teachings of Elbashir, outlined above, in designing siRNAs for experimental work. Only more recently has the use of chemical modifications become generally accepted.

Therefore, no motivation existed at the time of the invention to cleave VEGRr1 RNA using chemically modified siRNA molecules with 2'-O-methyl and 2'-fluoro modifications. In fact, because the *only* teaching in the cited art addressing the issue of the degree of modifications tolerated in siRNA molecules expressly states that more than a few end modifications should be avoided, it could not have been obvious to make the highly modified constructs now being claimed with a reasonable expectation of success.

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The present claims go directly against the express teachings of the art. Thus, due to the teachings of Elbashir I, there was no reasonable expectation of success in using chemically modified siRNA molecules with, *e.g.,* 2'-O-methyl and 2'-fluoro modifications. The cited references provide no enabling methodology for making chemically modified siRNAs with 2'-O-methyl and 2'-fluoro modifications, no suggestion to modify siRNA molecules to contain 2'-O-methyl and 2'-fluoro modifications and no evidence to suggest such modifications would result in an active siRNA molecule.

Furthermore, a reference cited to demonstrate obviousness must be analogous art. The reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 977 F.2d 1443, 1447 (Fed. Cir. 1992). Pavco is not analogous art and therefore does not form a proper basis of an obviousness rejection. Pavco teaches inhibition of flt-1 gene expression using antisense and ribozyme molecules. Pavco is not reasonably pertinent to chemically modified siRNA molecules that target VEFGr1. Antisense molecules are substantially single-stranded prior to interacting with their target, while siRNA is almost completely in a duplex form; it is well known to those skilled in the art that single-stranded nucleic acid is more susceptible to nuclease attack than is double-stranded nucleic acid. Antisense molecules will tolerate substantial 5' and 3' terminal modifications; in contrast the activities of siRNAs are almost completely destroyed by attaching modifications to the 5' end of the antisense strand of the siRNA. The activity of an antisense molecule is destroyed by modifications that alter the DNA-like structure at the core of molecule. It was not clear in 2001 whether the siRNA duplex would need to maintain an RNA-like structure or whether other structures would be permitted.

Likewise, ribozymes are non-analogous art to siRNA. The underlying premise of this rejection is the unstated and unsubstantiated assumption that all nucleic acid technology is essentially the same and interchangeable. The Office has conflated ribozyme and siRNA technology into "nucleic acid technology." This is evident in the

Office's application of ribozyme (Pavco) to the siRNA technology of Elbashir. What is missing from the rejection and what represents a fatal flaw in it is any teaching to this effect evident in the prior art at the priority date of the present application. Simply put, no evidence has been proffered indicating that chemical modifications employed in ribozyme technology could be freely and without limitation used in the siRNA technology of Elbashir with a reasonable expectation of yielding an active and useful siRNA construct. Yet, this is the basis of the present rejection.

Ribozymes are substantially single-stranded prior to interacting with their target, while siRNA is almost completely in duplex form; it is well known to those skilled in the art that single-stranded nucleic acid is more susceptible to nuclease attack than is double-stranded nucleic acid. Additionally, ribozymes will tolerate substantial 5' and 3' terminal modifications. In contrast, the activity of siRNA molecules is almost completely destroyed by attaching modifications to the 5' end of the antisense strand of the siRNA. Also, unlike siRNA molecules, ribozymes must form a complex RNA secondary structure to be active.

At the priority date of the present application, those of ordinary skill in the art understood that there were different structural features of nucleic acids required for activity in each of ribozyme and siRNA technologies because the mechanism of action of these nucleic acids differed in each. Significantly, the mechanism of siRNA had not yet been explored to the extent that one of ordinary skill in the art understood or could predict the effect of various types and positions of chemical modifications on the activity of a double stranded nucleic acid molecule. Absent such information, the patent owner respectfully submits that the present rejection amounts to nothing more than an assertion that the presently claimed constructs would be obvious to try. And it has been long recognized that the "obvious to try" standard is insufficient under 35 USC § 103.

Therefore, this combination of references does not teach or suggest the invention. Additionally, the scope and content of the prior art do not direct one of skill in the art to the present claims due to, *inter alia,* differences between the prior art and the claims at

issue. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection.

Claims 36-55 stand rejected under 35 USC § 103 as allegedly obvious over Pavco et al. (US 6,346,398 B1), in view of Elbashir et al. (EMBO J., 20:6877-6888, 2001), Parrish et al. (Molecular Cell, Vol. 6, 1077-1087, 2000), Cook et al. (US 5,587,471), Hammond et al. (Nature, 2001, vol 2, pages 110-119) and Caplan (Expert Opin Biol Ther, 2003 Jul, 3(4), pp.575-86) in further view of Agrawal (WO94/01550). Claims 37, 39-43 and 53-55 have been cancelled. The Applicants respectfully traverse with respect to claims 36, 38, 44-52, and 56-59.

The Office relies on the teachings of Parrish, Elbashir, Pavco, Hammond, Caplen, and Cook as described above. The Office also relies on Agrawal for its teaching of polynucleotide linkers. Agrawal does not correct the deficiencies of the Parrish, Elbashir, Pavco, Hammond, Caplen, and Cook references as described above. Therefore, this combination of seven references does not teach or suggest the invention. Applicants respectfully request withdrawal of the rejection.

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CONCLUSION

Applicant respectfully requests the claim amendments to be entered and the remarks considered. Applicant believes that with this amendment, the claims are in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of this application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff LLP

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